REMARKS

Claims 8-10 remain in the case.

Claims 8-10 were objected to by the Examiner under 35 USC 102(b) as being anticipated by or, in the alternative, under 35 USC 103(a) as being obvious over Poyet *et al.* (CA 121: 339, 1993).

The Examiner alleges that Poyet *et al.* teach that tBCEU (N-(2-chloroethyl)-N'-[4-(1,1-dimethylethyl(phenyl]-urea) affects the protein synthesis of two proteins present in the cytoskeleton of a human breast cancer cell line and therefore anticipates or makes obvious the instant claims.

The Applicants respectfully submit that Poyet *et al.* demonstrate that tBCEU increases the synthesis of some proteins including α-tubulin. At page 1448, (column 2, line 1) Poyet *et al.* state that "the results clearly indicate that tBCEU increase synthesis of at least 2 proteins: α-tubulin and vimentin". However, they do not demonstrate that tBCEU affects the level of expression of β-tubulin protein nor do they demonstrate any direct effect of the compound (*i.e.* alkylation) on β-tubulin protein.

Alpha and beta tubulin polypeptides constitute a multigene family of biochemically distinguishable isotypes. It has been demonstrated that the two different tubulin proteins (alpha and beta) play complementary roles. They are both essential in the formation of heterodimers, the unit which will polymerize with other heterodimers to form microtubules. Alpha and beta tubulins are under different regulatory mechanisms at the level of gene expression, posttranscriptional processing of mRNA and posttranslational modifications. Applicants respectfully submit that directly affecting β-tubulin generates defective heterodimers. Consequently, studies reporting the effect of a certain compound on increased α-tubulin synthesis does not anticipate the direct effects on □-tubulin.

As opposed to Poyet *et al.*, Applicants clearly demonstrate the □-tubulin inhibiting properties of certain CEU's. Furthermore, Applicants show that these CEU's are mild alkylating agents that covalently bind □-tubulin and prevent microtubule assembly. The requirements of both weak alkylating properties and hydrophobicity for

antineoplastic activity and β-tubulin alkylating capacity is also clearly demonstrated. Moreover, the CEU's of the present invention were shown to not significantly alkylate nucleophiles such as DNA, glutathione and glutathione reductase, which are targeted by most commercially available alkylating agents. These elements show the specificity and explain the low systemic toxicity of certain CEU's.

Additionally, Applicants have described the concept of "soft alkylation", which introduces new perspectives about the rational design of drugs that might be able to inactivate specific cellular proteins with resulting cytotoxic effects directed more specifically at tumor cells. Applicants respectfully submit that these findings are neither demonstrated nor anticipated by Poyet *et al.*

In light of the foregoing, Applicants submit that although the studies by Poyet *et al.* show an effect of tBCEU on the α-tubulin synthesis pathway, they do not indicate a direct or indirect effect on β-tubulin proteins and therefore do not render obvious or anticipate the effects of tBCEU on β-tubulin described by Applicants. It is therefore respectfully requested that the objection to claims 8-10 under 35 USC 102(b) and 35 USC 103(a) be withdrawn.

Favorable reconsideration of this application is earnestly solicited. The present application is believed to be in condition for allowance and a notification to this effect is earnestly solicited. A check in the amount of $210.00 is attached hereto to satisfy the government fee for the request for a two month extension of time. It is believed that no additional fees are due at this time, however should this determination be incorrect then please charge any deficiencies to our Deposit Account No. 13-2759 and notify the undersigned in due course. Should the Examiner wish to discuss this matter further, please contact the undersigned at the below listed number.

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